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**IN THE UNITED STATES PATENT & TRADEMARK OFFICE**

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| In re application of: Applicants | DeBenedetti, Arrigo, *et al.* | : Docket No: | 101611/507550 |
| Serial No. | 09/916,017 | : Group Art Unit: | 1635 |
| Filed: | July 26, 2001 | : Examiner: | J. Angell |

For: CANCER GENE THERAPY BASED ON TRANSLATIONAL CONTROL OF A SUICIDE GENE



**DECLARATION UNDER 37 CFR 1.132**

**Box Amendment Fee**
The Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This declaration under 37 CFR Sec. 1.132 is supportive of the Amendment and Response filed herewith. I, Robert Rhoads, Ph.D., declare and say:

1. That I am a citizen of the United States of America, that I have been employed by Louisiana State University Health Sciences Center-Shreveport since 1 July 1992, that I have been Department Head in the Biochemistry and Molecular Biology Department since 1 July 1992, and that I was and still am engaged in a research program in the field of cancer biology, specifically the mechanisms by which cells control growth and division;

2. That I am familiar with the above-identified patent application Ser. No. 09/574,734, that I have reviewed the April 24, 2002, Office Action in the above captioned case, and that I am familiar with the following references cited by the Examiner: DeFatta. (Dissertation; catalog and placed on the shelf March 20, 2001); Shimogori *et al.* (BBRC Vol. 223:544-548; 1996); Strathdee *et al.* (BioTechniques Vol. 28:210-214; 2000); and Kevil *et al.* (Oncogene Vol. 11:2339-2348).

3. That I disagree with the Examiner's position and maintain that one of ordinary skill in the field of molecular biology and medical science would find that the present specification is enabled for use in providing targeted treatment of tumors and it would be a routine matter to one skilled in the art to isolate RNA sequences that inhibit translation of an mRNA when placed upstream of the coding region in cells containing normal intracellular levels of eIF4E, yet allow translation of the mRNA in cells containing high intracellular levels of eIF4E, using the techniques disclosed in previous papers.

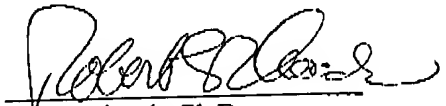
4. That, in the present case, the identifying characteristics of the specific DNA sequences that are claimed in the present invention are fully described in providing for those that, when transcribed, produce a messenger RNA sequence that comprises (a) a translatable sequence encoding a toxin, and (b) an untranslated sequence; wherein the untranslated sequence (i) inhibits translation of the toxin sequence at normal intracellular levels of eukaryotic initiation factor eIF4E, and (ii) wherein the untranslated sequence allows translation of the toxin sequence into a toxin in the presence of elevated eukaryotic initiation factor eIF4E.

5. That the specific functional characteristics of the claim sequences are an adequate representation of the genus and that the sequences that fall within the scope of the present claims are easily ascertained by any person of skill in the field of molecular biology and medical science, and that such person would know how to sequence various DNA sequences as well as how to test any particular sequence in order to determine whether the sequence inhibits translation of the toxin sequence at normal intracellular levels of eIF4E and allows translation of the toxin sequence into a toxin at elevated levels of eIF4E.

6. That in my opinion, it is well within the ability of person in the field of molecular biology and medical science to determine the appropriate sequences of the present invention for the following reasons: (1) the amount of testing required is relatively small especially since most of the work can be done with tissue culture experiments as the proof of principle with the animal studies was already provided; (2) testing of any particular sequence in question would not require direction or guidance beyond that known in the art; (3) the current state of knowledge in the art and relative skill of those in the art is quite high; (4) well-known procedures exist for sequencing various DNA sequences capable of producing a messenger RNA sequences that comprises an untranslated palindromic sequences; and (5) determining whether a sequence falls within the scope of the claims is quite straightforward, since all of the materials and methods that would be required to determine if a particular untranslated sequence inhibits translation of the toxin sequence at low intracellular levels of eIF4E and allows translation of the toxin sequence into a toxin at elevated intracellular levels of eIF4E are quite routine in the art.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth not.



Robert Rhoads, Ph.D.

23 Oct 02

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**DECLARATION UNDER 37 CFR 1.132**

**Box Amendment Fee**
The Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This declaration under 37 CFR Sec. 1.132 is supportive of the Amendment and Response filed herewith. I, Arrigo DeBenedetti, declare and say:

1. That I am a citizen of Italy, permanent resident USA, and that I am one of the co-inventors in the above-referenced patent application; that I have been employed by Louisiana State University Health Sciences Center-Shreveport since 1992 , that I have been Associate Professor (title) in the Biochemistry Department since 1998, and I was and still am, engaged in a research program in the field of cancer treatment and particularly dysregulation of Protein Synthesis;

2. That I am familiar with the above-identified patent application Ser. No. 09/574,734, that I have reviewed the April 24, 2002, Office Action in the above captioned case, and that I am familiar with the following references cited by the Examiner: DeFatta. (Dissertation; catalog and placed on the shelf March 20, 2001); Shimogori *et al.* (BBRC Vol. 223:544-548; 1996); Strathdee *et al.* (BioTechniques Vol. 28:210-214; 2000); and Kevil *et al.* (Oncogene Vol. 11:2339-2348).

3. That the inventorship of the current application is correct and that the DeFatta dissertation reference cited by the Examiner discloses subject matter derived from both myself and Robert J. DeFatta as co-inventors and not solely invented by the listed author of the publication notwithstanding the authorship of the article.

4. That I disagree with the Examiner's position and maintain that one of ordinary skill in the field of molecular biology and medical science would find that the present specification is enabled for use in providing DNA sequences claimed in the application and it

would be a routine matter to one skilled in the art to isolate untranslated mRNA sequences which inhibit translation of a gene in the absence of eIF4E and allows translation of the gene sequence in the presence of eIF4E using the techniques disclosed in previous papers.

5. That, in the present case, the identifying characteristics of the specific DNA sequences that are claimed in the present invention are fully described in providing for those that, when transcribed, produce a messenger RNA sequence that comprises (a) a translatable sequence encoding a toxin, and (b) an untranslated sequence; wherein the untranslated sequence (i) inhibits translation of the toxin sequence in the absence of eukaryotic initiation factor eIF4E, and (ii) wherein the untranslated sequence allows translation of the toxin sequence into a toxin in the presence of elevated eukaryotic initiation factor eIF4E.

6. That it would not have been obvious in any way to combine the Strathdee *et al.* reference with the Kevil *et al.* reference since it would not have been obvious to one skilled in the art that the 5'UTRs of the present invention linked to TK would in fact confer translational regulation to the TK mRNA. It was not known at the time that such 5'UTRs could regulate translation of a different reporter mRNA and it was not known at the time that tumor cells have high levels of eIF4E. Therefore, there would have been no motivation within the field to link translational regulation of HTK by the 5'UTR's of the present invention. Furthermore, at the time Kevil *et al.* was published it was not known that eIF4E was overexpressed in most tumors. As such, the benefit of regulating the translation of the mRNA to limit its expression in cancer cells overexpressing eIF4E could not be anticipated.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth not.

Arrigo DeBenedetti

10/23/02
Date

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